

Intensive Care Medicine

Risk of over-diagnosis of hypotension in children: a comparative analysis of over 50000 blood pressure measurements --Manuscript Draft--

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Author Comments:	<p>Dear Editor,</p> <p>Thank you for your consideration of the manuscript entitled 'Risk of over-diagnosis of hypotension in children: a comparative analysis of over 50000 blood pressure measurements'.</p> <p>We have previously presented these data to ICM in an Original Paper format (ICME-D-16-01926). We believe the size of the sample makes these data robust. we would be grateful for your consideration of the data presented more succinctly as a Letter, with a simple but powerful message regarding standard monitoring systems used in paediatric intensive care systems worldwide.</p> <p>We have also re-presented the data visually, with more information presented on the hypotensive cohort.</p> <p>Thank you</p>
Suggested Reviewers:	

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Risk of over-diagnosis of hypotension in children: a comparative analysis of over 50000 blood pressure measurements

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1 Maintaining a 'normal' blood pressure (BP) and avoiding hypotension are key goals in critically-ill
2 children [1]. Invasive arterial blood pressure (IABP) and non-invasive oscillometric blood pressure
3 (NIBP) measurements are typically used interchangeably despite reports of bias and lack of precision
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9 We compared concurrently recorded IABP and NIBP in 2 paediatric intensive care units (PICUs). Data
10 were collected from 2 sources: (a) the electronic health record (EHR) (Intellivue Critical Care and
11 Anaesthesia, Philips Electronics, Netherlands), typically recorded each hour (April 2009-October
12 2015 from one PICU; April 2012-December 2015 from the other), and (b) from the Etiometry T3
13 (Etiometry Inc., MA, USA) system, recorded directly from the patient bedside monitor at 5-second
14 intervals (June 2015-June 2016) in one PICU. While concurrence of measurement is assumed from
15 EHR data, this is guaranteed using high-resolution monitor data.
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27 After exclusion of 'out-of-range' values (systolic measurements <30 mmHg and >250 mmHg,
28 diastolic measurements <10 mmHg and >200 mmHg, and corresponding mean values), EHR data
29 were available from 2459 children, with pairs of 49404 mean, 50397 systolic, and 50266 diastolic BP
30 values.
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37 NIBP gave systematically lower readings for mean and diastolic BP than corresponding IABP.
38 Although statistically systolic NIBP were higher than IABP readings, the difference lacked clinical
39 significance. The biases (mean NIBP-IABP) were as follows: mean BP -9.2 mmHg (95%CI -9.3 to -9.1
40 mmHg, $p < 1 \times 10^{-11}$), systolic BP 1.0 mmHg (95%CI 0.8 to 1.1 mmHg, $p < 1 \times 10^{-11}$), diastolic BP -8.7
41 mmHg (95%CI -8.8 to -8.6 mmHg, $p < 1 \times 10^{-11}$) (Figure; diastolic data in Electronic Supplementary
42 Material). Precision, i.e. the 95% limits of agreement (interval within which 95% of NIBP-IABP values
43 lie), was poor: -31.8 and 13.4 mmHg for mean BP; -30.9 and 32.8 mmHg for systolic BP and -32.4 and
44 15.1 mmHg for diastolic BP. High-resolution T3 data from 253 children confirmed these findings
45 (Electronic Supplementary Material). A multi-level linear regression model failed to reveal a simple
46 relationship between patient age, weight or vaso-active medication use and bias.
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1 The main utility of BP monitoring in intensive care is to detect and respond to hypotension. If IABP is
2 considered as gold standard and hypotension defined as age-defined systolic BP <5th centile, NIBP
3 has poor positive predictive value (58.2%, 95%CI 57.3-59.1%) but good negative predictive value
4 (86.1%, 95%CI 85.8-86.5%) in detecting hypotension. While a 'normal' NIBP value is useful in ruling
5 out hypotension, treating hypotension based on an NIBP value can lead to over-treatment over 40%
6 of the time. The rule-in value of NIBP can be increased by repeating NIBP measurements. Using
7 Bayes theory (pre-test odd x likelihood ratio = post-test odds), 3 successive measurements of systolic
8 NIBP <5th centile increases the likelihood of the corresponding IABP being <5th centile to 96.3% (pre-
9 test odds of 0.31 x likelihood ratio of 4.42³ = post-test odds of 21, or post-test probability of 96.3%).
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22 These data demonstrate that use of low NIBP measurements in isolation to guide treatment for
23 hypotension in children could lead to over-treatment. Prospective studies of vital sign targets in
24 critically-ill children are urgently needed.
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31 **Ethical approval and consent to participate:** Ethical approval was not sought as we used routinely
32 collected clinical data retrospectively. Consent to participate was not sought as this is a retrospective
33 observational study and no patient identifiable data are presented.
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39 **Consent to publish:** Consent was not sought as no patient identifiable data are reported.
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42 **Availability of data and materials:** The datasets used and/or analysed during the current study
43 available from the corresponding author on reasonable request.
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46

47 **Competing interest:** The authors declare that they have no conflict of interest.
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51 **Author's contributions:** SR, MJP, SN and DPI conceived and designed the study; SR, LR, RD and DPN
52 collected and verified the data; SR and LR analysed the data. SR and DPI drafted the manuscript, all
53 authors contributed to and approved the final version of the manuscript.
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59 **Acknowledgements:** Not applicable
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Authors' information: DPI is the chief investigator and MJP and SN are co-investigators on the UK

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Figure: Bland-Altman plot of systolic (left) and mean (right) blood pressures using electronic health record data. For systolic blood pressure, non-invasive measurements have a low systematic bias (red line) (1.0 mmHg, 95%CI 0.8 to 1.1 mmHg, $p < 1 \times 10^{-11}$), but show poor precision, with 95% limits of agreement (blue lines) being -30.9 and 32.8 mmHg. The green dots show non-invasive measurements that were <5th centile for age (assuming 50th centile height as these data were not available). There is a skew towards negative values in this sub-population, demonstrating that non-invasive measurements tend to under-read blood pressure in the hypotensive range. For mean blood pressure, the bias is clinically significant (-9.2 mmHg, 95%CI -9.3 to -9.1 mmHg, $p < 1 \times 10^{-11}$), with equally poor precision (95% limits of agreement -31.8 and 13.4 mmHg). The green dots

represent non-invasive measurements <5th centile for age (and 50th centile of height): as with
systolic measurements there is a skew towards negative values.

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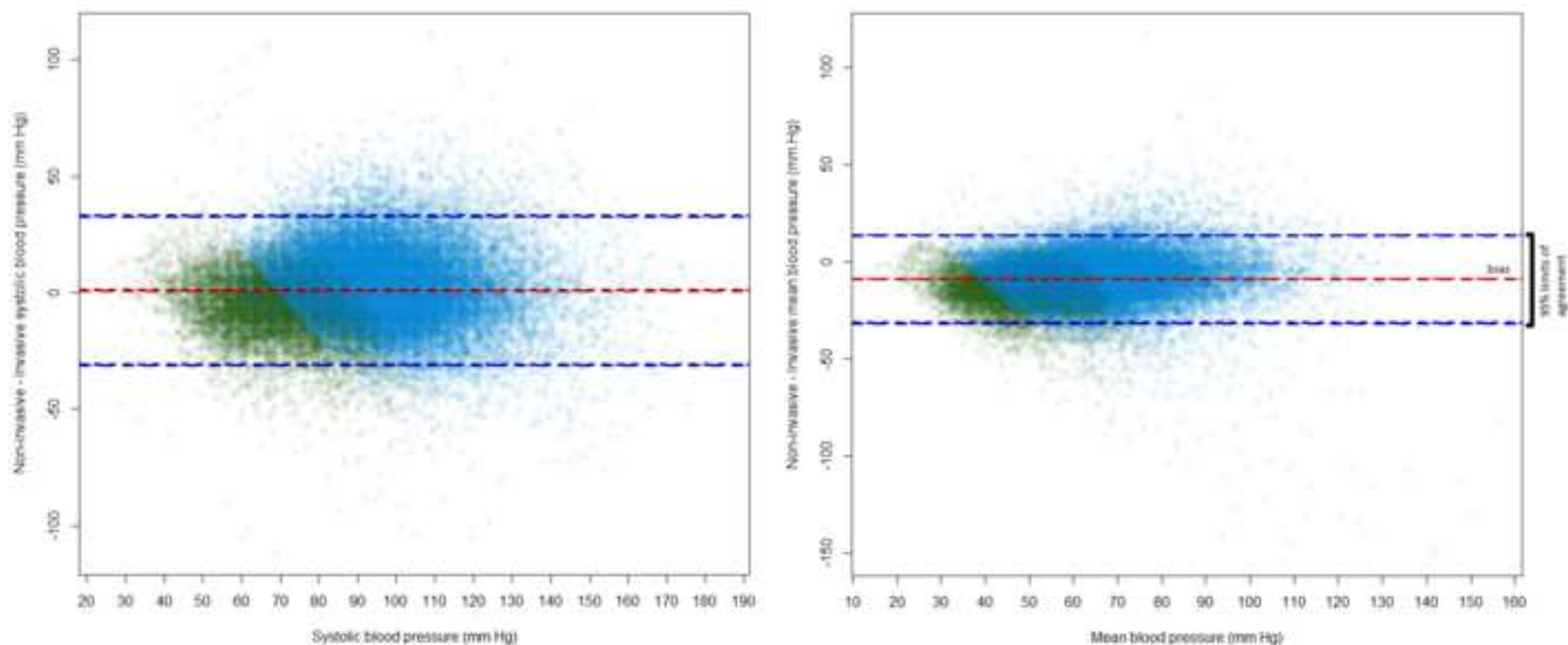
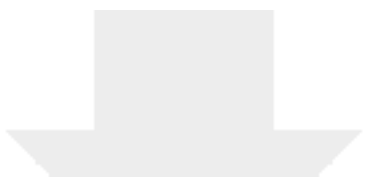


Figure: Bland-Altman plot of systolic (left) and mean (right) blood pressures using electronic health record data. For systolic blood pressure, non-invasive measurements have a low systematic bias (red line) (1.6 mmHg, 95%CI 0.8 to 2.4 mmHg, $p < 1 \times 10^{-10}$), but show poor precision, with 95% limits of agreement (blue lines) being -30.9 and 32.8 mmHg. The green dots show non-invasive measurements that were <5th centile for age (assuming 50th centile height as these data were not available). There is a skew towards negative values in this sub-population, demonstrating that non-invasive measurements tend to under-read blood pressure in the hypotensive range. For mean blood pressure, the bias is clinically significant (-3.2 mmHg, 95%CI -5.5 to -0.9 mmHg, $p < 1 \times 10^{-10}$), with equally poor precision (95% limits of agreement -31.8 and 25.4 mmHg). The green dots represent non-invasive measurements <5th centile for age (and 50th centile of height): as with systolic measurements there is a skew towards negative values.





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Supplementary Material
Figure ICM ESM2.tif

